DETAILED ACTION

Claims 16-20, 24-30,33-55 are pending and claims 18-20, 24-30, 33-53 are considered on the merits. Applicant has elected the species of organ and CO.

The previous office action has been withdrawn. A new office action appears below.

Election/Restrictions

Newly submitted claims 54, 55 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: they are directed to treating disease states, while the original method claims are directed to treating donors/recipients or organs during transplantation procedures.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 54, 55 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

ENABLEMENT

Claims 18-20, 24-30, 33-53 remain/are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the transplantation of any organ with administration of CO and NO. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The invention, in one embodiment, is directed to the transplantation of organ(s), which is the elected species. This term is interpreted in the common scientific sense of a differentiated structure composed of tissues and cells.

The claims encompass the transplantation of any organ with the treatment of the recipient with administration of both CO and NO. The claims are interpreted in plain language which means that both CO and NO, which are gases, are administered, not the administration of chemical compounds which release these gases in an indirect fashion nor transfer of genes which increase the concentration of these compounds *in vivo*. The terms donor and recipient are interpreted to include humans as well as other animals.

There is no working example directed to transplantation of any organ. The working examples are directed to (a) a cell culture treatment of isolated hepatocytes with CO or to protection of mice against acute liver failure induced by TNF-α/D-gal with CO, which is a mouse model of fulminant hepatic failure (hepatitis). Even for this model, no concomitant administration of CO and NO is demonstrated. No art accepted transplantation model is presented which demonstrates superior survival or function of transplanted liver or any other organ when CO with NO is administered to the recipient.

With regard to liver transplantation, Bishop *et al.* [V] teaches that liver has a better transplantation rate in rodents even when mismatched unlike other organs such as heart. Thus, liver is an organ which exhibits a less stringent matching requirement than other organs. Kanoria *et al.* [W] also discuss models for liver transplantation which include global ischemia. Because liver may one of the most forgiving organs to transplant and no art accepted animal model for liver transplantation is presented, it is not reasonable to use results obtained with an *in vitro* liver culture model to predict that a patient receiving other organs can benefit from the treatment of the claimed method prior to, during or after transplantation.

Meade *et al.* [AU] disclose that administration of NO to the human recipient of a lung transplant had no effect on the outcome of the transplantation procedure (abstract). The concentration of NO administered was 20 ppm, initiated 10 minutes after reperfusion of the lung and maintained at 20 ppm during surgery, then at a dosage of 10 ppm for 6 hours

postoperatively.

Applicants teach that the administration of NO may be at a concentration of about 0.1ppm to about 300ppm and the preferred dosage range is from 10ppm-100ppm. The duration of the dosage is at least one hour to at least 5 years, page 13.

Thus, given the evidence presented in Meade *et al.* [AU], where even the dosage and duration of NO administration are within applicants teachings, no benefit of the administration of NO to the human recipient of a lung transplant was found.

Akamatsu *et al.* [U] is directed to a rat model of ischemia after exposure of hearts to cold prior to transplantation. Akamatsu *et al.* administers CO to the heart transplant recipient at 400 ppm. Akamatsu *et al.* conclude that "Administration of CO to the recipient without further treatment or in combination with CO administration to the donor and/or the graft during ischemia did not show a significant additional affect...(page 771). And again on page 772, "on the other hand, exposure of the recipient to CO at the time of reperfusion does not afford a significant improvement in protecting hearts from IRI".

Applicants teach on page 27 that the administration of CO may be at a concentration of 10-1000 ppm and preferably about 200 to about 500ppm.

Thus, evidence given in Akamatsu *et al.* where the dosage administered is within the ranges given by the applicant, show that no benefit accrued in a rat model of transplantation from the administration of CO to the recipient.

Further, Bauer *et al.* [V] state while experimental evidence strongly suggests a beneficial effect [of the administration of CO] under pathophysiological conditions such as organ transplantation, ischemia/reperfusion, inflammation, sepsis, or shock states, the few human studies available do not support the promising results observed in experimental

studies. The protective effects of exogenous CO may strongly depend on the pathological condition, the mode, time point and duration of application, the administered concentration and on the target tissue and cell.".

Although the specification discloses methods of administration of NO and CO *in vitro*, to a liver cell culture, there are no data on the effectiveness of CO and NO being administered to a transplant recipient and used in a therapeutic treatment of liver or other organ injury due to ischemia, reperfusion and immunogenicity which are some of the types of injury which occur during and after transplantation of a liver or other organ.

As the separate and individual administration of CO and NO to transplant recipients have been shown to be unpredictable, for the reasons discussed above, it is considered that the co-administration of both NO and CO to a transplant recipient is also unpredictable. The combination of two unpredictable treatments, in the absence of evidence, is not considered to make the claimed treatment predictable.

Therefore, in view of the nature of the invention, the state of the prior art, the amount of guidance present in the specification and the breadth of the claims, it would take undue experimentation to practice the claimed invention with regard to the variables of organ type, species of recipient, concentration of administered NO and CO, duration of administration, and time of administration.

Response to Arguments

Applicant's arguments filed 2/11/09 have been fully considered but they are either moot because of the new construction of the enablement rejection or are not persuasive.

Applicant presents a review that CO administration to rats and mice has a positive effect on transplantation results (Nakao *et al.* 2006). While this evidence has been considered, the claims are not limited to rats and mice administered CO alone.

Applicants assert that there are many factors associated with the failure of the administration of NO by Meade *et al.*, such as improper timing of the NO administration, improper NO dosage, etc.. The examiner agrees and these are also parameters which produce unpredictability in the practice of the invention over the scope of the claims.

Applicants urge that the results presented using models of inflammation in mice demonstrate there is a synergism between CO and NO in providing cytoprotection, which they are the first to show. However, no showing of synergism in an animal model is found in the specification.

Presentation of appropriate objective evidence might promote prosecution.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information

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/Sandra Saucier/
Primary Examiner
Art Unit 1651